The Furan-2(5*H*)-ones: Recent Synthetic Methodologies and its Application in Total Synthesis of Natural Products

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Abstract: In recent years, furan-2*(5H)*-ones have attracted considerable attention as synthetic target. This subunit is present in a large number of natural products, which display a wide range of biological activities, and is present in a number of drugs with diverse biological activities, such as antifungal, antibacterial and anti-inflammatory. It can also be used as synthetic intermediate. This review describes recent synthetic methodologies for preparation of furan-2*(5H)*-ones, as well as their application in the total synthesis of natural products with this subunit.

Keywords: Furan-2(5*H*)-ones, biologic activity, natural products, synthetic methodologies.

INTRODUCTION

In recent years, furan-2*(5H)*-ones (Fig. **1**) have attracted considerable attention as synthetic targets. This ring system, known also as furanone or butenolide [1], occurs as structural subunits in a large number of natural products isolated from many sources including sponges and algas [2], animals [3], plants [4], butterflies [5] and others insects [6]. Those compounds display a wide range of biological activities, such as antimicrobial [7], antifungal [8], anti-inflammatory [9], anticancer [10], anti-viral HIV-1 [11], phytotoxic [12], cardiotonic [13], insecticidal [14], pheromonal effects [15], antifedant [16] and cyclooxygenase or phospholypase A_2 inhibitors [17]. This ring system has also been the target of many synthesis due its potential pharmaceutical and industry proprieties [18], as intermediate in synthesis of antibodies, as selective catalysts [19], as dopants for ferroelectric liquid crystals [20] and as monomers for ring-opening polymerization to generate polyesters as potential piezo-electric material [21]. Due to the importance of the butenolides in many fields, much attention has been paid to develop synthetic methodologies for their preparation. The aim of the present article is to make a review that covers the literature from 1998 to present date of recent and important synthetic methodologies for the preparation of furan-2*(5H)*-ones, as well as the total synthesis of natural products containing this subunit.

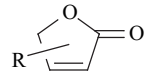
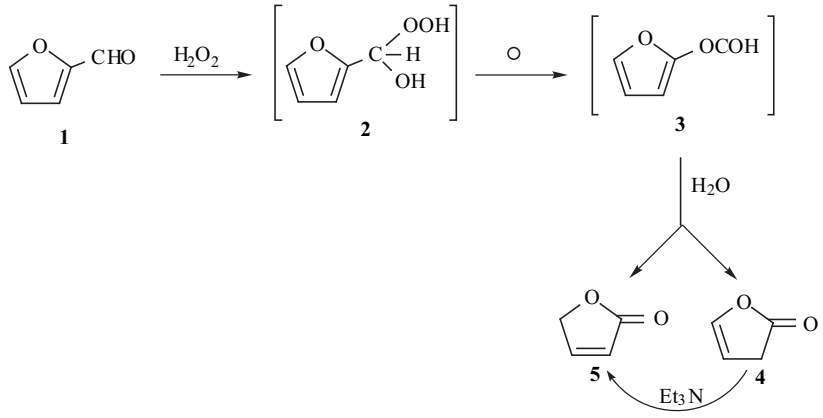


Fig. (1).

1. SYNTHESES OF FURANONES FROM FURAN PRECURSORS

The furan precursors are a useful synthon for preparation of furanones. For example, the 2*(5H)*-furanone was easily prepared by Liu *et al.*, who described a convenient method, which involved refluxing furfural **1** and hydrogen peroxide in dichloroethane and sodium sulfate (Scheme **1**) [22]. The oxidation afforded a mixture of 2(3H)-furanone **4** and 2*(5H)*-furanone **5**, which was separated by distillation. Isomerization of **4** with triethylamine provided **5** in good yield (Scheme **1**).



Scheme 1.

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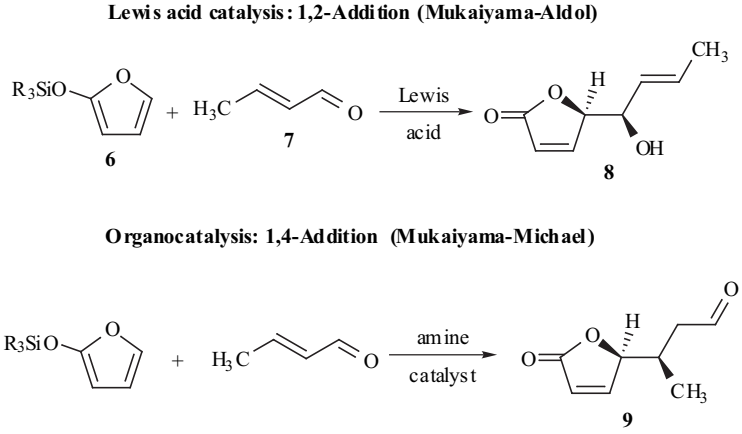


Scheme 2.

The furan is also a valuable synthon for the preparation of γ-butenolides (Fig. **2**). This subunit is present in over 13.000 natural products [23] and a valuable architectural platform for the development of new asymmetric methodologies [24]. In this context, the catalytic coupling of silyloxy furans **6** and aldehydes using chiral Lewis acids [25] and organocatalysis [26] has emerged as an excellent strategy for butenolide synthesis (Scheme **2**).

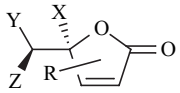
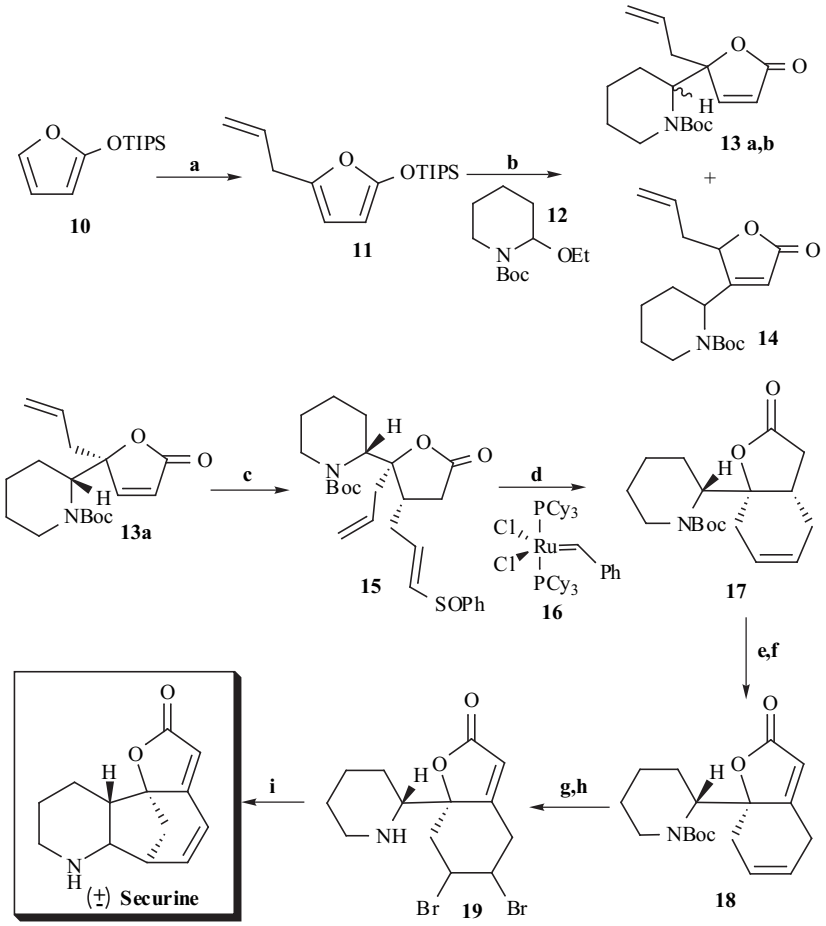


Fig. (2).

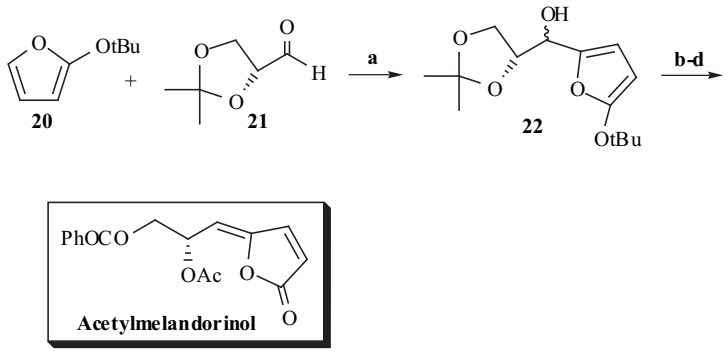
The total synthesis of natural products containing 2*(5H)*-furanone is largely prepared from furan precursors [1, 27]. The total synthesis of the alkaloid securinine design by Liras



Scheme 3. a) *sec*-BuLi, TMEDA, allyl bromide, THF, 0ºC, 82%; b) TIPSOTf, heptane, -78ºC; **12**, 78% c) allyl phenyl sulfoxide, LiHMDS, THF, -78ºC to – 45ºC, 71%; d) Gubbs catalyst **16**, 1,2-dichloroethane, 70ºC, 79%; e) LiHMDS, THF, phenyl selenyl bomide, -78ºC to rt; f) H_2O_2, dichloromethane, 0ºC, 43% for two steps; g) TFA, dichloromethane; h) bromine, chloroform, -10ºC to rt; i) K_2CO_3, DMF, 70ºC, 78% for three steps.

et al. [28] is a good example (Scheme **3**). This natural product is a member of the Securinega family of alkaloids, and in addition to its interesting structure, which contains and indolizidine skeleton, a butenolide moiety, and an azabicyclo [3.2.1] system, securine also possesses CNS biological activity as a GABA receptor antagonist [29]. The concise total synthesis of securine accomplished by Lira *et al*. was achieved in nine steps from readily available starting materials (Scheme **3**). The first step of the Liras synthesis involved the preparation of silyloxyfuran **11**, which was produced in 82% yield upon treatment of the readily available silyloxyfuran **10** [30] with *sec*-BuLi and TMEDA at 0ºC in heptane followed by addition of ally bromide (Scheme **3**). The preparation of silyloxyfuran **11** set the stage for its addition to an iminium ion generated *in situ* from the readily available 2-ethoxy piperidine derivative **12** [31]. The ideal reaction conditions, which minimized the formation of furanone **14** were discovered when a mixture of furan **11** and the piperidine **12** in heptane at –78ºC was treated with 0.1 equiv. of TIPSOTf. These reaction conditions furnished the butenolides **13a,b** and **14** in a ratio of 8:2:1, respectively (Scheme **3**). These furanones were separated by flash chromatography and the synthon **13a** was used to prepare the compound **15** by treatment of excess of the allyl phenyl sulfoxide with LiHMDS. Subsequently, the substrate **15** was used in a ring closing metathesis reaction in presence of an excess of the Grubbs reagent **16** to produce the key intermediate **17** in 79% yield (Scheme **3**). The treatment of **17** with LiHMDS and phenyl selenyl bromide followed by oxidative elimination in presence of hydrogen peroxide furnished the compound **18** in 43% yield (two steps). The total synthesis of securine was subsequently achieved after removal of the nitrogen-protecting group of **18** with trifluoroacetic acid (TFA) and treatment of the crude product with bromine to afford the dibromide **19**. Finally, the crude dibromide **19** in presence of K_2CO_3 yielded securinine in 78% yield (three steps) (Scheme **3**).

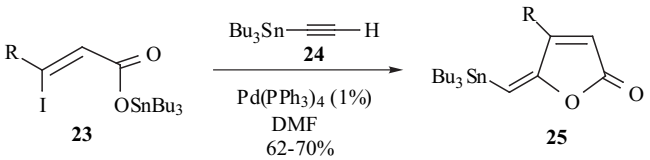
Another example using furan as starting material is the enantioselective synthesis of acetylmelodorinol made by Shen *et al.* [32] (Scheme **4**). The acetylmelodorinol was isolated from *Melodrum fruticosum Lour (Annonaceae)* [33] and showed cytotoxic activities in several human tumor cell lines including breast carcinoma, lung carcinoma and colon adenocarcinoma. The lithiation of the alkoxyfuran **20** and subsequent reaction with the glyceraldehydes **21** provided two diastereoisomers **22** in 69% yield, which were treated with *p*-toluenesulfonic acid to furnish a γ-propylidene butenolide in 74% yield. Then, selective benzoylation of the primary alcohol was accomplished with benzoyl cyanide that also provided the natural product melodorinol in 54%, which was acetylated to furnish the acetylmelodorinol in 63% yield (Scheme **4**).



Scheme 4. a) **20**, *t*-Buli, THF, 69%; b) TsOH, THF, H_2O, 74%; c) PhCOCN, Et_3N, THF, -40ºC, 54%; d) Ac_2O, pyridine, CH_2Cl, 63%.

2. TRANSITION METAL-CATALYZED PROCESS

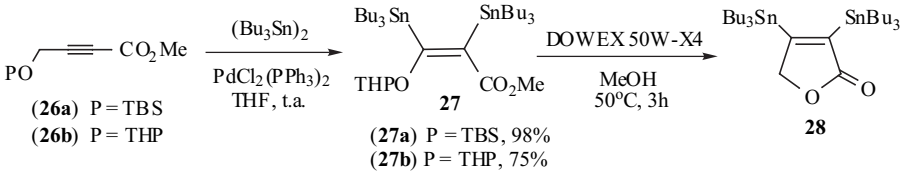
The use of transition metal complexes as catalysts for organic transformations is currently the subject of intense activity. In this context, palladium catalysis has achieved the status of an indispensable tool in the modern organic synthesis with important synthetic applications. For example, palladium catalyzed methods are currently, the most frequently used method for preparation the substituted 2*(5H)*furanones [33] with wide application in total synthesis of natural products. A good example of the construction of butenolide using palladium-catalyzed is the stereoselective synthesis of *(E)*-γ-tribuylstannylmethylidene butenolides **25** that was achieved by Duchêne, Parrain *et al.* using the palladium-catalyzed tandem cross-coupling/cyclization reactions (Stille reactions) of tributylstannyl 3-iodopropenoate derivatives **23** with tributyltinacetylene **24** in 62-70% yield (Scheme **5**).



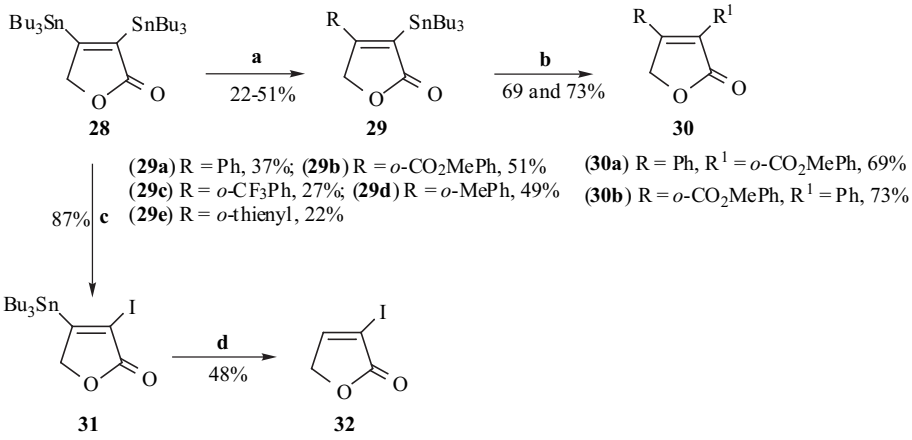
R = **a**) H; **b**) Me; **c**) $MeOCH_2$-; **d**) Ph; **e**) Me_3Si.

Scheme 5.

Sweeney *et al.* reported in detail [34] the first preparation of 3,4-bistributylstannyl 2*(5H)*-furanones **28**. The preparation of this compound commenced with the bisstannylation of butynoate **26a,b** that reacted with hexabutylditin in the presence of $PdCl_2(PPh_3)_2$ to give the 2,3-bis(tri-butylstannyl)acrylate **27a,b** in 98% and 75% yield, respectively (Scheme **6**). Unfortunately under a variety of reaction conditions **27a** could not be converted to **28**. In order to solve this problem, the analogous THP-protected bis(stannane) **27b** was prepared using the same reaction conditions in 75% yield from propynoate **26b** and subsequently, upon reaction with acidic ion-exchange resin



Scheme 6.



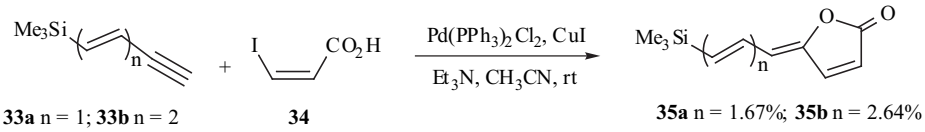
Scheme 7.

in methanolic solution the hydroxyl group of **27b** was unmasked and cyclization occurred to furnish lactone 28 as a colorless liquid in 74% yield (Scheme **6**).

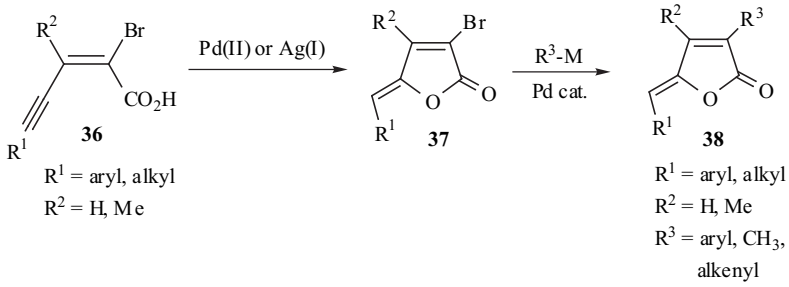
Sweeney *et al.* also demonstrated in detail that the regioselective Stille reaction of bis(stannane) **28b** allows the preparation of 4-substituted 3-stannyl-2*(5H)*furanones 29a-e in 22-51% yield (Scheme **7**), which can then be converted into disubstituted furanones **30a,b** in **69** and 73% yield, respectively (Scheme **7**). In contrast, Sweeney *et al.* observed that the C_3-Sn bond was more nucleophilic by its selective reaction with iodine, which produced the intermediate **31** in 87% yield (Scheme **7**).

Fiandanese *et al.* reported an efficient and stereoselective approach to a variety of silylated polyunsaturated (Z)-γ-alkylidene butenolides [35] (Scheme **8**). This methodology was based upon Pd(II) catalyzed cross-coupling/cyclization reaction, which can be successfully elaborated for the construction of conjugated unsaturated butenolides.

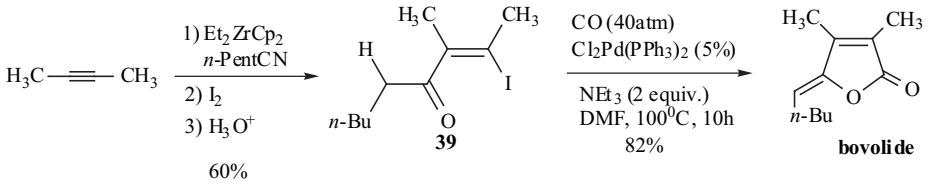
Silver is also a good reagent to furnish butenolides from ynoic acids by catalytic lactonization in mild conditions and high yields [36]. For example, Rossi *et al.* developed a general procedure for the preparation of 3-substituted and 3,4-disubstituted (Z)-5-ylidene-*5H*-furan-2-ones **37** and **38** [7,37] (Scheme **9**). This methodology involves a Pd (II) or Ag (I)-mediated cyclization of easily available (E)-3-(1-alkynyl)-2-bromopropenoic acid **36**, followed by a Pd-catalyzed cross-coupling reaction of the resultant (Z)-3-bromo-5-ylidene-*5H*-furan-2-ones **37** with a organic zinc or an organic tin compound [37] (Scheme **9**).



Scheme 8.



Scheme 9.

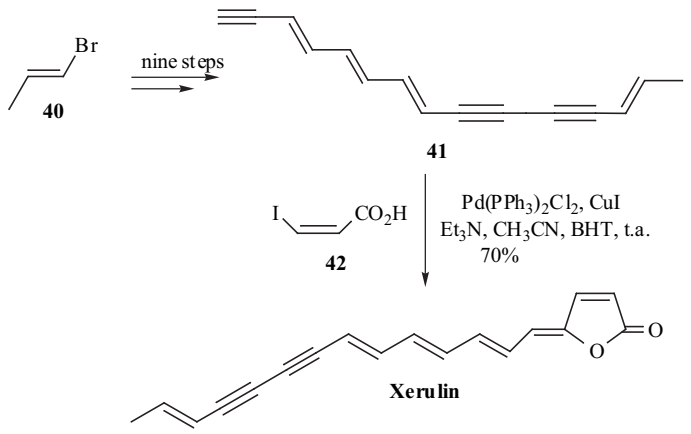


Scheme 10.

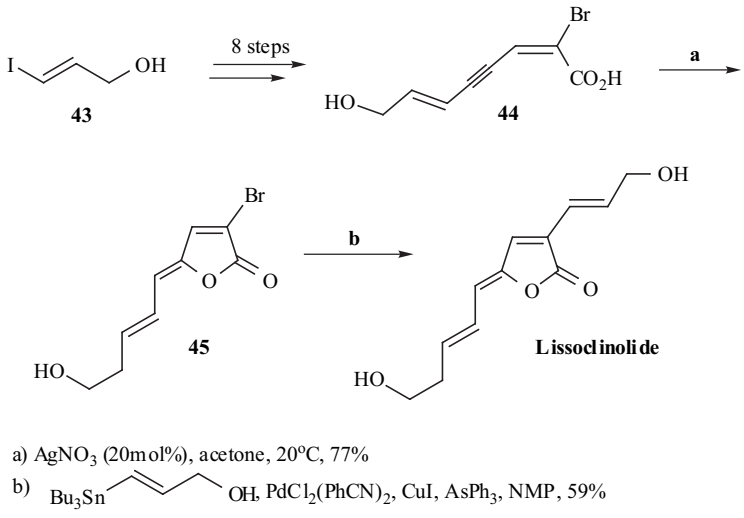
Transition metal catalyzed reactions represent a useful method for the preparation of a variety of natural products containing butenolide system. In this context, the total synthesis of the natural product bovolide designed by Negishi *et al.* was successfully achieved using Pd-catalyzed carbonylative method [38] (Scheme **10**). A two-step synthesis of bovolide from 2-butyne, hexanenitrile, and CO in 50% overall yield and ≥ 98% stereoselectivity illustrates the potential synthetic application of the transition metal catalyzed reactions (Scheme **10**).

Another good example of the transition metal catalyzed reactions in total synthesis is the Pd(II) catalyzed cross-coupling/cyclization reaction in the synthesis of the natural product xerulin produced by Negishi and co-workers [39]. Xerulin is a polyenynyl (*Z*)-γ-butenolide containing six C=C and two C≡C bonds in conjugation, isolated from *Xerula melanotricha Dorfelt* [40], and it is an inhibitor of cholesterol biosynthesis. The Negishi group reported an efficient and stereoselective total synthesis of xerulin (Scheme **11**) requiring only five steps (longest linear sequence) in 30% overall yield and >96% stereoselectivity. This synthesis was achieved in ten total steps starting from commercially available (*E*)-1-bromopropene, acetylene and propynoic acid. The key step reaction was between tetraenetriyne **41** and (*Z*)-3-iodoacrylic acid **42** using a sequential *one-pot* Sonogashira-cyclization that furnished the xerulin in 70% yield (Scheme **11**).

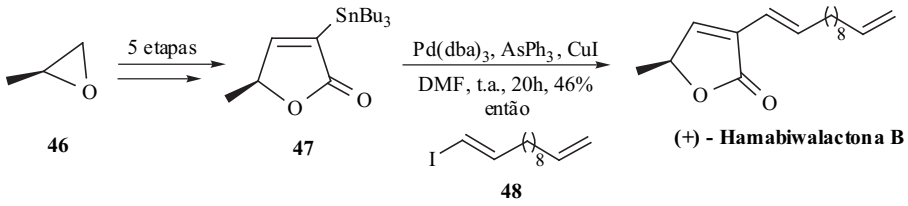
Silver was also used successfully in total synthesis for the preparation of butenolides. For example, Rossi *et al.* described a stereocontrolled total synthesis of lissoclinolide using Ag(I) mediated cyclization as a key step [7] (Scheme **12**). Lissoclinolide is a (*Z*)-5-ylidene-*5H*-furan-2-one isolated



Scheme 11.



Scheme 12.



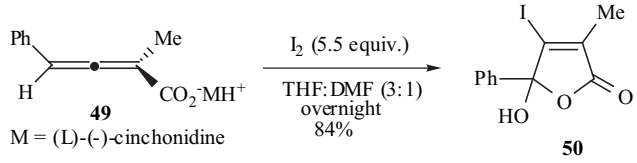
Scheme 13.

from *Lissoclinum patella*, which exhibits activity against the bacterium *Escherichia coli* [41]. The key step reaction involves the compound 44 in presence of catalytic amount of Ag(I) that produced by cyclization the furanone **45** in 77% yield [7]. Subsequently, by a Pd-catalyzed cross-coupling reaction (Stille reaction) between **45** and (*E*)-3-tributylstannylpropenol the lissoclinolide was obtained in 59% yield (Scheme **12**).

Based on their experience in cross-coupling reaction of 3- and 4-stannylfuranones, Sweeney *et al.* accomplished the first total synthesis of Hamabiwalactone B in high enantioselective (Scheme **13**) [42]. This natural 2(5*H*)-furanone was isolated from the roots of *Litsea Japonica* (Japanese name Hamabiwa), which grows in the southern part of Japan [43]. The Sweeney synthesis has been achieved using the (+)-(*S*)-propylene oxide **46** as start material, which after five steps furnished stannylfuranone **47**. The key step of Sweeney synthesis was a palladium-catalyzed cross coupling (Stille reaction) between the (5*S*)-methyl-3-tributyl-stannyl 2(5*H*)-furanone **47** and the previously synthesized (*E*)-1-iodododeca-1,11-diene **48**, which produced the Hamabiwalactone B in 46% yield and with the enantiomeric purity of ≥ 99% (Scheme **13**).

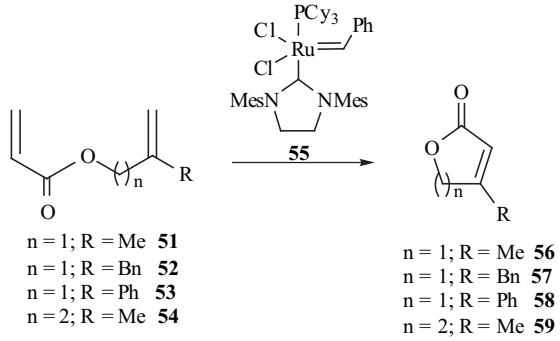
3. MISCELLANEOUS METHODS

Recently, different new synthetic methodologies have been discovery for preparation of furan-2*(5H)*-ones, with potential application in the total synthesis of natural products containing this subunit. For example, as 5-hydroxyfuran-2(*5H*)-ones are often found in natural products and exhibit a broad range of biological activity [44], Ma *et al.* synthesized 5-halo-5-hydroxyfuran-2(*5H*)-ones (Scheme **14**) *via* the efficient sequential halolactonization hydroxylation reaction of 4-aryl-2,3-allenoic acids **49** with I_2 to produce the intermediate **50** in good yield [44].



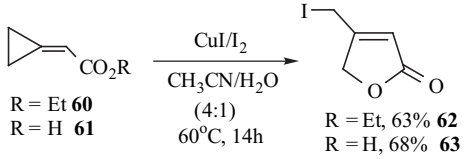
Scheme 14.

Buchwald *et al.* describe a preparation of lactones by an operationally simple and inexpensive ring-closing metathesis (RCM) methodology of the dienes **51-54** with good perspectives for application in the total synthesis of natural products [45] (Scheme **15**). Compounds **51-54** were prepared by esterification of allylic alcohols and subsequent treatment with 2 mol % of ruthenium carbene **55** furnished lactones **56-59** after 2h in refluxing dichloromethane with 95% of conversion [45].



Scheme 15.

Huang *et al.* introduced a facile and effective copper-mediated cyclization reaction of cyclopropylideneacetic acids **60** or esters **61** with CuI/I_2 that can produce 4-iodomethyl-2-(*5H*)-furanones **62** and **63** in aqueous acetonitrile at 60ºC for 14h [46] (Scheme **16**).



Scheme 16.

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